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EXAMINER	
AFREMOVA, VERA	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 12/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/937,137	SITAR, GIAMMARIA
	Examiner	Art Unit
	Vera Afremova	1651

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1 and 3-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1 and 3-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9/17/2003*.

4) ☐ Interview Summary (PTO-413) Paper No(s). _____.

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: .

DETAILED ACTION

Claims 1, 3-6 as amended and new claims 7-9 are pending and under examination.

Claim 2 is canceled by applicant.

Claim Objections

Claim 9 is objected to because of the following informalities:

Claim 9 is drawn to the use of a device as illustrated on fig. 1 that appears to be identical to the device that is claimed in US 6,309,606. It is suggested to use claim language identical to the claim language in US 6,309,606 to avoid possible claim rejection under 35 U.S.C. 112, second paragraph.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 1, 3-6 as amended and new claims 7-9 remain/are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 7 are indefinite with respect to identifying step because it is uncertain what are the "appropriate" identifications procedures that are claimed. The claimed method is directed to isolating/preparing fetal cells from maternal blood cells. But the identifying step as claimed does not point out what "appropriate" identification procedures for separation and/or identification, are intended. Thus, the method as claimed appears to be incomplete.

Claims 1 and 7 are indefinite and uncertain with regard to the components of "tissue culture medium" because it is uncertain what components of this medium would modify the mixture comprising "tissue culture medium", "maternal blood" and "aqueous solution" so that

the final "mixture" would have the claimed characteristics. For example: it is uncertain what would be a source of 400-500 mg glucose in one dl of the final "mixture". Neither "tissue culture medium" nor "aqueous solution" clearly indicates the inclusion of glucose. The claimed amounts of glucose are above normal concentration of glucose in blood or plasma that are about 100 mg/dl as evidenced by Guyton [U] (see page 277, Fig. 25-4 or see page 752, col. 2). Thus, claims 1 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted element is a source of glucose.

Claim 9 is indefinite because it is uncertain what features illustrated on Fig. 1 are included and/or excluded from the instantly claimed invention.

Claims 1, 3-6 as amended and new claims 7-9 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention.

Claims 1 and 7 are drawn to incorporation of dextran into "aqueous solution" but it appears that the intended subject matter is drawn to incorporation of glucose or dextrose but not dextran.

Evidence that claims 1 and 7 fail(s) to correspond in scope with that which applicant(s) regard as the invention can be found in the specification as-filed and in the priority document MI99A000652. In the as-filed specification of the instant US application the claimed "tissue culture medium" is the medium as disclosed in table 2 pages 8-9. However, this medium does not contain glucose. Yet, the claimed invention encompasses the glucose amounts that are clearly higher that might be present in normal blood, for example: 100 mg/dl as evidenced by Guyton

[U]. Thus, it is reasonably to conclude that glucose has to be added to the blood sample. However, the instant claims do not point out what is a source of the claimed amounts of glucose. The claimed invention suggests that the only other possible source of glucose might be an "aqueous solution" which contains "dextran" as presently claimed. The instant specification also indicates that "aqueous solution" contains "dextran" but not glucose or dextrose (page 9, line 3). The priority document MI99A000652 can not be properly evaluated because it is not in English, for example: see page 13, lines 2-3, but it appears that the subject matter is drawn to the use of dextrose or glucose but not dextran.

Nevertheless, the prior art of record (US 5,676,849 at col. 6, line 58) demonstrates that the similar "aqueous solution(s)" that are employed in the methods for separation of fetal and maternal cells contain glucose or dextrose but not dextran that is claimed. Thus, it is considered that the presently claimed invention is failing to set forth the subject matter, which applicant(s) regard as their invention with respect to the contents of "aqueous solution(s)". In alternative, the claimed invention is missing some structural element related to the source of glucose or dextrose.

Please, note that where a non - English foreign priority document under 35 U.S.C. 119 is of record in the application file, applicant may not rely on the disclosure of that document to support correction of an error in the pending application. Ex parte Bondiou, 132 USPQ 356 (Bd. App. 1961). This prohibition would apply regardless of the language of the foreign priority documents because a claim for priority is simply a claim for the benefit of an earlier filing date for subject matter that is common to two or more applications, and does not serve to incorporate the content of the priority document in the application in which the claim for priority is made. This prohibition does not apply in a situation where the original application is in a non - English

language (37 CFR 1.52(d)), or where the original application explicitly incorporates a non - English language document by reference. MPEP 2163.07.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1 and 3-8 are rejected under 35 U.S.C. 102(a) as being anticipated by Sitar et al. {Cytometry, April 1, 1999. Vol. 35, No. 4, pages 337-345.}

Claims are directed to a method for isolating or preparing fetal nucleated red blood cells (NRBCs) present in maternal peripheral blood for prenatal genetic investigation wherein the method comprises step of combining a maternal blood sample with a tissue culture medium and an aqueous solution comprising citrate in order to form a mixture having specific characteristics that are pH 6.4-6.6, osmolarity 300-330 mOsm, Na^+ 150-160 mmol/l, K^+ 4.5-5.5 mmol/l, Cl^- 100-115 mmol/l, Ca^{++} 1.00 –2.50 mmol/l, glucose 400-500 mg/dl, lactate 10-20 mg/dl; step of transferring the mixture to a cell separation device and adding a high density liquid containing a red blood cell aggregating agent, step of isolating NRBCs by subjecting the separation device to centrifugal force, step of washing and resuspending the isolated NRBCs and step of identifying and counting fetal NRBCs. Some claims are further drawn to the use of a liquid containing a red blood cells aggregating agent such as Ficoll containing preparation. Some claims are further drawn to the use of a liquid in separation device with 1.068 g/ml density. Some claims are

further drawn to the use a cell separation device or apparatus in a method for isolating fetal cells present in maternal peripheral blood for prenatal genetic investigation.

The reference by Sitar et al. {April 1, 1999} discloses substantially the same, if not identical, method for isolating or preparing fetal nucleated red blood cells (NRBCs) present in maternal peripheral blood for prenatal genetic investigation. The method as disclosed by the cited reference comprises identical active steps including step of forming a mixture comprising maternal blood sample, tissue culture medium RPMI-1640 and an aqueous solution with citrate and dextrose; step of transferring the mixture to a cell separation device and adding a high density liquid containing a red blood cell aggregating agent including Ficoll, step of isolating NRBCs by subjecting the separation device to centrifugal force including the use of solution density 1.068 g/ml, step of washing and resuspending the isolated NRBCs and step of identifying and counting fetal NRBCs. For example: see Fig. 2 and see page 338, col. 2, par. 2. The cited reference teaches the value of pH 5.5-7.5 of the resulting mixture that is subjected to centrifugation and osmolarity 260-330 mOsm (page 339, col. 1, lines 25). The cited reference clearly teaches that a decrease in pH causes beneficial improvements in separation of NRBCs (see Fig. 2).

Although the cited reference is silent with regard to the precise values of Na^+, K^+, Cl^-, Ca^{++}, glucose and lactate, these values are reasonably expected to be the substantially the same, if not identical, as presently claimed. The claimed amounts for Cl^-, Ca^{++}, and lactate are the same as in normal blood sample as evidenced by Guyton. Thus, the blood sample of the cited reference provides for the same amounts in the resulting mixture. The claimed amounts for Na^+ and K^+ are about the same or slightly higher than in normal blood. But the tissue culture medium RPMI-

1640 is reasonably expected to provide for additional inorganic salts because the basic RPMI-1640 medium is known to contain sodium and potassium. The claimed amounts of glucose are higher than in normal blood. But the aqueous solution with citrate and dextrose (glucose) is reasonably considered to provide for additional glucose (dextrose). Therefore, the characteristics of the final mixture are substantially the same, if not identical, as presently claimed. Thus, the cited reference is considered to anticipate the applicant's invention as intended and/or as claimed.

The cited reference teaches the use of separation device with elongated chamber and opening (Fig. 1) or the use of other commonly used devices (page 339, col. 1, last par.). Thus, the cited reference anticipates that claimed invention as drawn to the use of a generic separation device of claim 6.

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1 and 3-5, 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,641,628 [D] taken with US 5,676,849 [B], US 5,432,054 [C] and Guyton [U].

The cited patent US 5,641,628 [D] is relied in the instant office action for the disclosure of methods for isolating nucleated fetal cells from maternal peripheral blood intended for prenatal genetic investigation (example 10) wherein the method encompasses isolation of fetal

nucleated red blood cells by density gradient centrifugation of maternal blood which has been modified by addition of citrate dextrose aqueous solution (col. 22, line 42). The cited patent also teaches steps of transferring the mixture to a cell separation device, adding a high density liquid with Ficoll, step of isolating mononuclear cells including NRBCs by subjecting the separation device to centrifugal force, step of washing and resuspending the isolated cells and step of identifying fetal NRBCs with antibodies to precursors of hematopoietic cells and by PCR techniques with Y chromosome primers.

The cited patent US 5,641,628 [D] is silent with regard to the final characteristics of the modified blood sample. However, the claimed amounts for Cl^-, Ca^{++}, and lactate are the same as in normal blood sample as evidenced by Guyton (page 277). Thus, the blood sample of the cited patent US 5,641,628 provides for the same amounts for Cl^-, Ca^{++}, and lactate in the resulting blood mixture as encompassed by the claimed invention. The reference by Guyton also demonstrates that osmolarity of normal blood is about 302 mOsm that is within the presently claimed ranges. Thus, the blood sample of the cited patent US 5,641,628 provides for the same osmolarity as encompassed by the claimed invention. Further, osmolarity in the method of the cited patent US 5,641,628 [D] is reasonably expected to be increased after addition of the aqueous citrate-dextrose solution. The presently claimed amounts for Na^+ and K^+ are about the same or slightly higher than in normal blood according to the reference by Guyton. But the citrate aqueous solution of the cited patent US 5,641,628 [D] is likely to provide for additional sodium and/or potassium. The cited patent US 5,641,628 [D] also suggests that the blood sample is stored overnight with the culture medium RPMI (col. 13, line 42) and, thus, the blood sample is reasonably expected to contain about the same amounts of potassium and/or sodium as

encompassed by the claimed invention. The cited patent US 5,641,628 is silent about pH value. But the cited patent US 5,676,849 [B] demonstrates that the commonly used citrate-dextrose/glucose aqueous solution contain citric acid (col. 6, line 58 or col. 10, lines 39). Thus, the solution in the method of US 5,641,628 [D] is reasonably expected to provide for pH low that neutral in the method for fetal cells preparation or identification.

The cited patent US 5,641,628 [D] teaches the separation of cells by liquid density gradient centrifugation but it is silent about the liquid density in the method for separation of fetal cells from maternal blood. However, the cited patent US 5,432,054 [C] teaches the use of liquid density gradient centrifugation for separation of fetal cells from maternal blood wherein the liquid density gradient includes 1.065 g/ml (col. 12, table 2) or about 1.068 g/ml for centrifugation of modified maternal blood as encompassed by the presently claimed method.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to practice a method for isolating fetal cells present in maternal peripheral blood for prenatal genetic investigation wherein the method encompasses isolation of fetal nucleated red blood cells by density gradient centrifugation of maternal blood modified by addition of acid-citrate-dextrose (glucose) preparation as taught and suggested by the cited patents US 5,641,628 [D] and US 5,676,849 [B] with a reasonable expectation of success in isolating fetal nucleated red blood cells as demonstrated by the cited patents. The concept of isolating fetal cells from maternal blood of the cited patents US 5,641,628 [D], US 5,676,849 [B] and US 5,432,054 [C] is based on a density gradient centrifugation isolation of fetal nucleated red blood cells from modified maternal blood and it is similar to the concept of the presently claimed method which is also based on a density gradient centrifugation isolation of fetal

nucleated red blood cells from modified maternal blood. The characteristics of the resulting modified blood sample that are claimed appear to be about the same as encompassed by the cited US 5,641,628 [D] as evidenced by Guyton. Although the cited patent(s) are lacking the particular disclosure about dextran, the final characteristics of the modified blood sample that are claimed are not affected by dextran whether it is added or not to the blood sample. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary. One of skill in the art would have been motivated to used acid-citrate-dextrose solution for the expected benefits in blood cell separation because addition of this aqueous solution is a common practice in the methods for separation of fetal cells from maternal blood as adequately demonstrated by the cited US 5,641,628 [D] and US 5,676,849 [B]. Thus, the claimed subject matter fails to patentably distinguish over the state art as represented be the cited references.

Therefore, the claims are properly rejected under 35 USC § 103.

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,641,628 [D] taken with US 5,676,849 [B], US 5,432,054 [C] and Guyton [U] as applied to claims 1, 3-5, 7 and 8 above, and further in view of US 4,424,132 [D], GB 2-75376 [N] and FR 77 08053 [O].

Claims 1, 3-5, 7 and 8 as explained above. Claim 6 is further drawn to the use of a cell separation device or apparatus with elongated chamber and channel(s) that are open to the chamber in a method for isolating fetal cells present in maternal peripheral blood for prenatal genetic investigation.

The cited patents US 5,641,628 [D], US 5,676,849 [B] and US 5,432,054 [C] are relied upon as explained above for the disclosure of methods for isolating nucleated fetal cells from maternal peripheral blood intended for prenatal genetic investigation wherein the methods encompass isolation of fetal nucleated red blood cells by density gradient centrifugation of modified maternal blood in various cell separation devices. The cited patents are silent about design of cell separation devices. However, the methods of the cited patents encompass the use of generic cell separation devices and they result in successful separation of fetal cells. Thus, there is a reasonably believe that the cell separation devices of the cited patents are suitable and appropriate in the methods for isolating nucleated fetal cells from maternal peripheral blood intended for prenatal genetic investigation.

Additional references US 4,424,132 [D], GB 2-75376 [N] and FR 77 08053 [O] are relied upon to demonstrate a large variety of cell separation devices available in the prior art and suitable for cell separation in the present invention directed to a method for isolating nucleated fetal cells from maternal peripheral blood intended for prenatal genetic investigation. The devices of the cited patents comprise an elongated chamber and channel(s) that are open to the chamber.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use a large variety of cell separation devices suitable for separating blood cells including isolating nucleated fetal cells from maternal peripheral blood intended for prenatal genetic investigation as demonstrated by the cited references. The cited references are in the same field of endeavor and seek to solve the same problems as the instant application and claims such as blood cell separation, and one of skill in the art is free to select

devices available in the prior art. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary. Moreover, the devices disclosed by the cited patents US 4,424,132 [D], GB 2-75376 [N] and FR 77 08053 [O] are admitted by applicant as suitable in the presently claimed invention (specification page 6, par. 3). Thus, whatever differences might exist between various cell separation devices of the prior art and the particular device of the present invention, the claimed subject matter fails to patentably distinguish over the state art as represented by the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,641,628 [D] taken with US 5,676,849 [B], US 5,432,054 [C] and Guyton [U] as applied to claims 1, 3-5, 7 and 8 above, and further in view of WO 99/23471 {14 May 1999}.

Claims 1, 3-5, 7 and 8 as explained above. Claim 9 is further drawn to the use of a particular cell separation device as illustrated on Fig. 1 of the instant application.

The cited patents US 5,641,628 [D], US 5,676,849 [B] and US 5,432,054 [C] are relied upon as explained above. They are lacking the disclosure of a device as illustrated on Fig. 1 of the instant application. But WO 99/23471 {14 May 1999} teaches that use of device that is identical to the device as illustrated on Fig. 1 of the instant application and that is intended for separation of cells from mixed cell populations including cells of hematopoietic lineage as intended in the instant method for fetal cell separation from maternal blood cells.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use device that is identical to the device as illustrated on Fig.

1 for separating blood cells including isolating nucleated fetal cells from maternal as suggested by WO 99/23471 for separation of various cells of hematopoietic lineage. The cited references are in the same field of endeavor and seek to solve the same problems as the instant application and claims such as blood cell separation, and one of skill in the art is free to select devices available in the prior art. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary. Moreover, the device disclosed by WO 99/23471 is admitted by applicant as suitable in the presently claimed invention (specification page 6, par. 3). Therefore, the claims are properly rejected under 35 USC § 103.

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Response to Arguments

Applicant's arguments with respect to claims as amended and new claims have been considered but are moot in view of the new ground(s) of rejection.

Claim rejection over US 5,663,052 [A] has been withdrawn in the instant office action because US 5,663,052 does not appear to teach and/or suggest forming a resulting mixture with the presently claimed characteristics, for example; pH as argued by applicant. The cited patents do not disclose the use of solution similar to the acid-citrate aqueous solution, and, thus, it does not appear to teach and/or suggest the acid pH in the resulting blood mixture.

With regard to US 5,676,849 [B] and US 5,432,054 [C] the applicant's arguments as drawn to the red cell lysis disclosed therein are not found convincing because the claimed method does not exclude lysis of at least some adult red blood cells or maternal blood red cells

by the virtue of the language "comprising" and by the virtue of the language "non-physiological" mixture.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (703) 308-9351 till January 15, 2004 or (571) 271-0914 after January 15, 2004. The examiner can normally be reached on 9.30 am - 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (703) 308-4743 till January 15, 2004 or on (571) 272-0926 after January 15, 2004.

The fax phone number for the TC 1600 where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Vera Afremova V. Afremova

AU 1651 VERA AFREMOVA

December 18, 2003. PATENT EXAMINER